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Medications for Diabetes and Cardiovascular Disease Management

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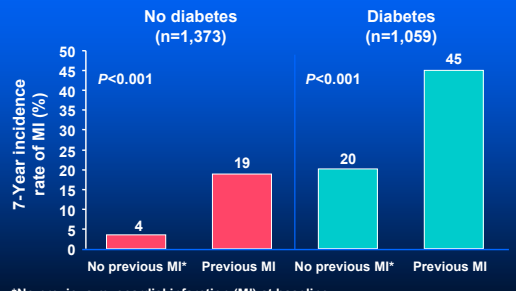
Objectives

- Discuss the relationship of diabetes with cardiovascular disease
- List specific goals of treatment for blood pressure and cholesterol in persons with diabetes
- Describe medications recommended for use for blood pressure, lipid lowering, and cardiovascular protection effects for persons with diabetes
- Review some of the newer diabetes medications

3

Seven-Year Incidence of Fatal/Nonfatal MI in Finland



*No previous myocardial infarction (MI) at baseline.

Haffner SM et al. *N Engl J Med.* 1998;339:229-234.

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Prevention of CVD

- ACEIs?
  - HOPE
- ARBs?
  - LIFE
- Combination of ACEIs and ARBs
  - ONTARGET and TRANSCEND

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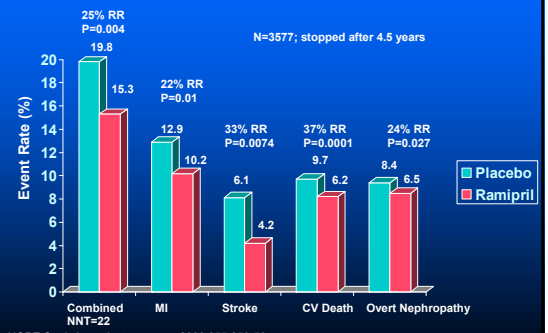
HOPE and MICRO-HOPE: Outcomes in DM Patients



HOPE Study Investigator. *Lancet* 2000;355:253-59.

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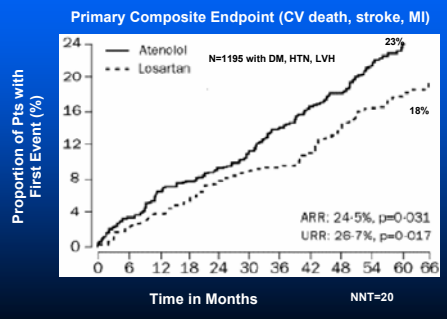
Losartan Intervention for Endpoint Reduction in HTN



LIFE Study Group: *Lancet* 2002;359:1004-10.

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Ongoing Trials

- ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)
  - Do an ARB or ACEI or combo confer BP-independent cardioprotection in high risk pts whose BP is well-controlled?
- TRANSCEND (The Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease)
  - Telmisartan vs. placebo in ACEI intolerant persons
- Primary endpoint for both: composite of CV death, MI, stroke, and hospitalization for CHF
- Randomized to: telmisartan 80 mg, ramipril 10 mg/d, telmisartan 80 mg/d + ramipril 10 mg/d

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Prevention of CVD (DM)

- Statins
  - HPS: Yes
  - CARDS: Yes
- Fibrates
  - VA-HIT: Yes
- Niacin
  - HATS: Yes
- TZDs
  - PROACTIV: Yes, BUT Controversial

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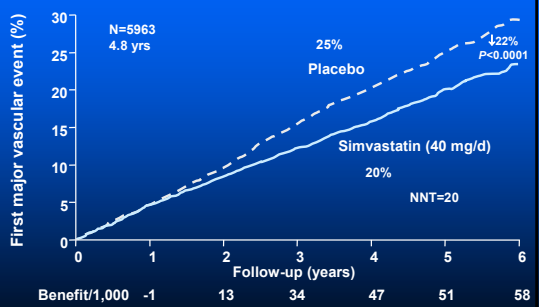
HPS Substudy: First Major Vascular Event in Patients With Diabetes



HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.

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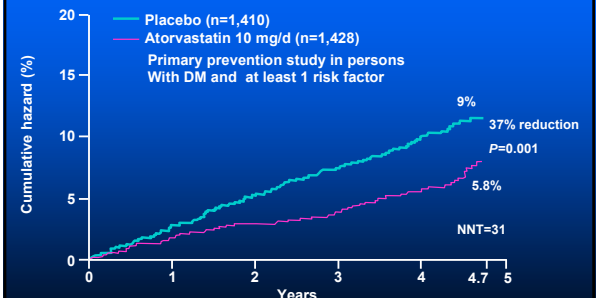
CARDS: Major CVD Events



CARDS=Collaborative Atorvastatin Diabetes Study

Colhoun HM et al. *Lancet*. 2004;364:685-696.

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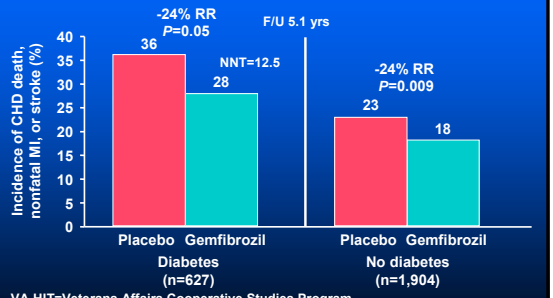
VA-HIT: Effect of Gemfibrozil on Vascular Events



VA-HIT=Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial

Rubins HB et al. *N Engl J Med*. 1999;341:410-418.

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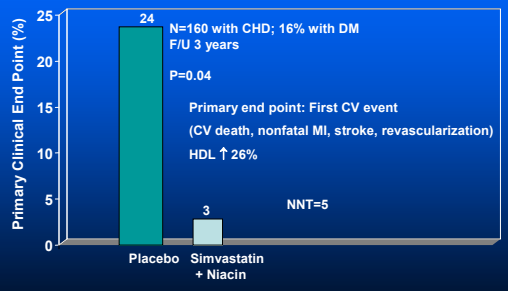
HATS Trial



Brown BG et al. N Engl J Med. 2001;345:1583-92.

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PROactive: Objective/Endpoints

PROactive=Prospective Pioglitazone Clinical Trial in Macrovascular Events.

To assess the effect of pioglitazone as add-on therapy on rates of CVD events in high-risk patients with type 2 diabetes and CVD

- **Primary composite endpoint:**
  - all-cause mortality
  - nonfatal MI (including silent MI)
  - stroke
  - acute coronary syndrome
  - cardiac intervention (including PCI/CABG)
  - major leg amputation
  - leg revascularization
- **Main secondary composite endpoint:**
  - all-cause mortality
  - nonfatal MI (excluding silent MI)
  - stroke

N=5238; F/U 2.8 yrs

Charbonnel B et al. *Diabetes Care*. 2004;27:1647-1653.

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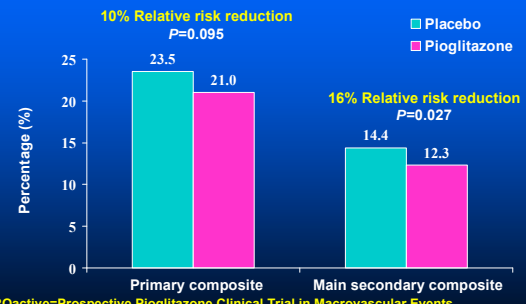
PROactive: Primary and Main Secondary Endpoint Results



PROactive=Prospective Pioglitazone Clinical Trial in Macrovascular Events.

Dormandy JA et al. *Lancet*. 2005;366:1279-1289.

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PROactive: Heart Failure Events

Endpoint	Pioglitazone n (%)	Placebo n (%)
Reported HF (nonadjudicated) (*P*<0.0001)	281 (10.8)	198 (7.5)
HF leading to hospitalization (*P*=0.007)	149 (5.7)	108 (4.1)
HF leading to death (*P*=0.034)	25 (0.96)	22 (0.84)

Dormandy JA et al. *Lancet*. 2005;366:1279-1289.

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Hypertension in Diabetes

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Prevalence

- Hypertension affects 65 million Americans; 30% of the adult population
- Nearly 75% of adults with diabetes take antihypertensive medication or have a blood pressure ≥ 130/80 mmHg
- Hypertension affects 50% of people with type 2 diabetes at time of diagnosis

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Epidemiology and Complications of HTN and DM

- Epidemiological studies have shown a correlation between elevated blood pressures and cardiovascular disease (stroke, myocardial infarction, angina, heart failure, or early death).
- Compared to the general population, people with diabetes have a 2-4 fold increased risk of cardiovascular disease
- Concomitant hypertension triples the high risk of cardiovascular disease (CAD), doubles total mortality and stroke risk, and may be responsible for up to 75% of all CVD events in people with diabetes.

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Complications of HTN and DM

- Accelerates the progression of diabetic
  - Nephropathy
  - Retinopathy
  - Neuropathy
- SBP is a stronger predictor than diastolic blood pressure for both CVD and renal complications.

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CVD Risk Factors

- Hypertension*
- Cigarette smoking
- Obesity* (BMI ≥ 30 kg/m^2)
- Physical inactivity
- Dyslipidemia*
- Diabetes mellitus*
- Microalbuminuria or estimated GFR < 60 ml/min
- Age (older than 55 for men, 65 for women)
- Family history of premature CVD (men under age 55 or women under age 65)

*Components of the metabolic syndrome

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HTN Treatment and Diabetes

- ADA Target BP
  - < 130/80 mm Hg
- Most hypertensive patients with diabetes will require a combination of two to three antihypertensive agents to lower blood pressure to target goal

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New 2007 AHA BP Targets

Indications	BP Goal (mm/Hg)	Initial Tx	Beta-blockers
Low CAD Risk	<140/90	ACEI, ARB, CCB, thiazide	Not first line
High CAD Risk	<130/80	ACEI, ARB CCB, thiazide	Not first line
With CAD	<130/80	BB and ACEI or ARB	Use first line
Heart failure	<120/80 if possible	BB, ACEI or ARB, diuretics, and aldosterone antagonist	Use first line

Circulation 2007;115:2761-88.

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Antihypertensive Choices

- Diuretics
- Beta blockers
- ACEIs (angiotensin converting enzyme inhibitors)
- ARBs (angiotensin receptor blockers)
- Calcium channel blockers
- Alpha agonists
- Alpha-1 blockers
- Direct vasodilators

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Lifestyle Modification to Lower Blood Pressure

Modification	Potential ↓ in Systolic/Diastolic Blood Pressure (mmHg)
10-lb weight loss	7/6
Dietary Approaches to Stop Hypertension diet (DASH)	11.4/5.5
Restriction of alcohol consumption Men: ≤ 2 drinks/day Women: ≤ 1 drink/day	3.9/2.4
Exercise: 30-60 minutes/day, 4-7 days/week	4.9/3.7
Restrict dietary sodium to < 1.4 g/day	3.4/1.9

JAMA 2002;288:1882-8.

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Effect of Antihypertensives On Adult Diabetes Patients

Class	Effects on coronary events rates*	Effects on Renal disease progression	Effects on stroke
Thiazide diuretics	Beneficial (A)*	Unknown	Beneficial (A)
Loop diuretics	Unknown	Unknown	Unknown
Central-acting adrenergic agents	Unknown	Unknown	Unknown
Beta-Blockers	Beneficial (A)	Beneficial (A)	Beneficial (A)
Alpha-Blockers	Controversial	Unknown	Unknown
DHP CCBs	Controversial	Controversial	Beneficial (A)
NDHP CCBs	Unknown	Beneficial (C)	Unknown
ACE inhibitors	Beneficial (A)	Beneficial (A)	Beneficial (A)
Angiotensin-2 antagonists	Unknown	Beneficial (A)	Unknown

*Level of evidence for summary

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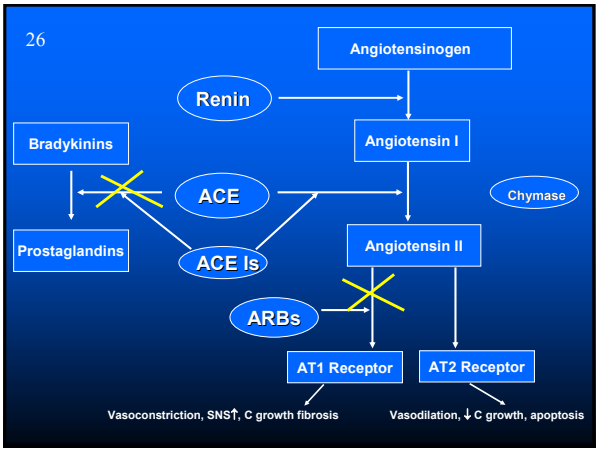

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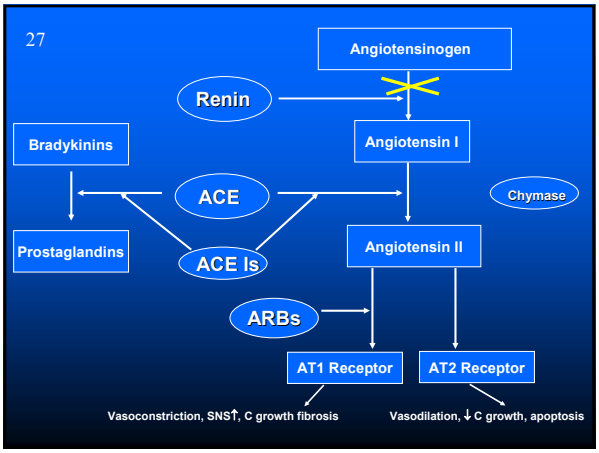

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Direct Renin Inhibitor (DRI) Tekturna® (Aliskiren)

- MOA
  - Directly inhibits renin
    - Renin is secreted in response to decreased blood volume and renal perfusion
    - Renin controls first step of the RAAS – cleaving Angiotensinogen to Angiotensin I
    - Inhibits renin from cleaving Angiotensinogen to Angiotensin
      - This ↓circulating levels of Angiotensin II
  - Reaches steady state in about one week

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Tekturna® (Aliskiren)

- ADRs
  - Diarrhea (at higher dose and in women and elderly)
  - Cough – less common
  - Rash – less common
  - Angioedema (Rare)
  - Teratogenicity

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Tekturna® (Aliskiren)

- Mainly metabolized through CYP3A4
  - Hence theoretical induction or inhibition by inducers or inhibitorsI
- Drug Interactions
  - Irbesartan ↓ aliskiren Cmax by up to 50%
  - Atorvastatin ↑ aliskiren Cmax by 50%
  - Ketoconazole ↑ aliskiren SDCs by 80%
  - Aliskiren ↓ AUC and Cmax of furosemide by 30% and 50% (respectively)
  - No significant interactions with lovastatin, atenolol, cimetidine, warfarin, or celecoxib

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Tekturna® (Aliskiren)

- Dose
  - 150 mg daily; may ↑ to 300 mg daily
- May be used as monotherapy or combined with HCTZ 25 mg or amlodipine 5 mg to ↑ antihypertensive efficacy
- Has also been studied in combination with ACEIs and ARBs – jury is out as to potential combination recommendations
  - Most experience in combination is with diuretics and ARBs

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Tekturna® (Aliskiren)

- Place in therapy
  - Not known yet
  - Being studied in combination with other drugs, include ACEIs and ARBs
    - May see increased K
  - More complete inhibition of RAAS than ACEIs or ARBs
  - DM or renal disease?

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ADA Clinical Practice Recommendations Treatment of HTN in Adults with Diabetes (2003)

- Type 1 Diabetes w/ or w/o HTN, with any degree of albuminuria (A)
  - ACEI- shown to delay progression of nephropathy
- Type 2 Diabetes with HTN and microalbuminuria (A)
  - ACEI and ARBs - shown to delay progression to macroalbuminuria
- Type 2 Diabetes with HTN and macroalbuminuria (>300 mg/day), nephropathy, or renal insufficiency (A)
  - ARBs - strongly considered
- If one class is not tolerated, the other should be substituted (A)

Diabetes Care 2003;26:S80-S82

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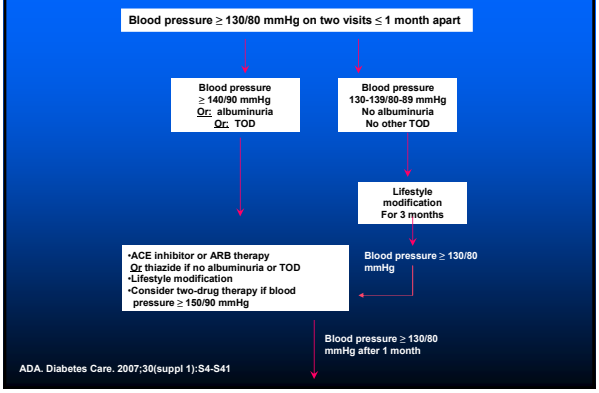
Algorithm for Treatment of Hypertension in Patients with DM (No Heart Failure and Not Post-MI)



ADA. Diabetes Care. 2007;30(suppl 1):S4-S41

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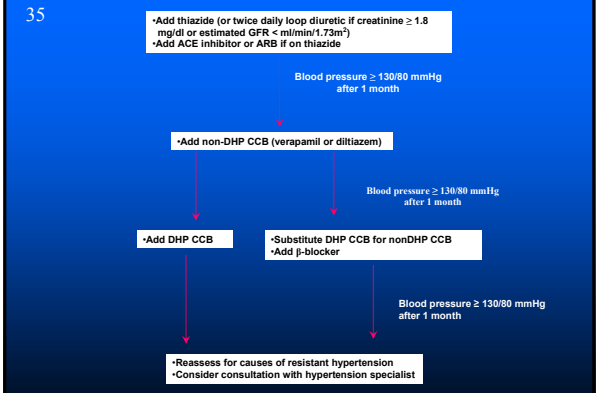

ADA. Diabetes Care. 2007;30(suppl 1):S4-S41

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Antihypertensives Used In DM

- ACE Is, ARBs
  - Monitor BP, BUN, Cr, K, cough
- Thiazides
  - Monitor BP, electrolytes
- Non-DHP CCBs
  - Monitor BP, HR (↓), ECG
  - Caution when used with beta blockers
- Beta blockers
  - Monitor BP, HR (↓), ECG
  - Caution when used with non-DHP CCBs
- DHP CCBs
  - Monitor BP, HR (↑)

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Summary of BP Control in DM

- Intensive control of blood pressure reduces cardiovascular morbidity and mortality in patients with diabetes
- ACE-inhibitors and ARBs are the drug of choice, however thiazides, BB, CCBs are viable options and should be considered unless contraindicated
- A combination of more than 1 drug is frequently required to control blood pressure to <130/80 mm Hg and may be more beneficial than monotherapy

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Lipid Control in DM

- Test for lipid disorders at least annually
  - More often if needed to achieve goals
  - If low risk, may consider testing ever 2 years
- Goals
  - LDL < 100 mg/dL (if no CVD)
    - 10% ↑ associated with 20% ↑ in CHD risk
  - LDL < 70 mg/dL if overt CVD
  - HDL > 40 mg/dL (males); > 50 mg/dL (females
  - TG < 150 mg/dL

ADA. *Diabetes Care*. 2007;30(suppl 1):S4-S41.

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Lipid Control in DM

- If TG > 200 mg/dL, target non-HDL cholesterol
  - Non HDL = Total Cholesterol – HDL
  - Goal is 30 mg/dL higher than goal LDL (e.g., if goal LDL is < 100 mg/dL, goal non-HDL is < 130 mg/dL)

ADA. *Diabetes Care*. 2007;30(suppl 1):S4-S41

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Lipid Control in DM

- If no overt CVD and > 40 y/o
  - Goal LDL is still < 100 mg/dL
  - But consider statin to ↓ LDL by of 30-40% regardless of baseline LDL
- If < 40 y/o but at ↑ CVD risk
  - Lifestyle first
  - Consider pharmacological agent if lipid goals not achieved with lifestyle

ADA. *Diabetes Care.* 2007;30(suppl 1):S4-S41

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Lipid Control in DM

- If overt CVD
  - Treat with a statin to ↓ LDL by of 30-40%
  - Treat with high dose statin (if necessary) to achieve LDL < 70 mg/dL
  - ↓ TGs to < 150 mg/dL and ↑ HDL to > 40 mg/dL (males) or > 50 mg/dL (females)
- Combination treatment with statins + other agents may be necessary
- Always include lifestyle measures

ADA. *Diabetes Care.* 2007;30(suppl 1):S4-S41

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Lipid Control in DM

- Lifestyle measures
  - ↓ saturated fat – changed to monounsaturated fat
  - ↓ trans fat, cholesterol (No > 200 mg/dL per day)
  - ↓ ETOH consumption (if excessive)
  - ↑ soluble fiber (oat, bran, vegetables, fruits)
  - ↓ weight (if indicated)
  - ↑ physical activity
- Consider plant stanols/sterols
  - Examples: Benecol®/Take Control®
  - 5-15% ↓ in LDL
    - But may ↓ absorption of fat-soluble vitamins (A,D,E,K)

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Mechanism of Antihyperlipidemics

- Statins
  - Inhibit HMG Co A reductase (rate-lowering step in cholesterol synthesis)
  - Up-regulate LDL receptors
- Fibrates
  - ↑ lipoprotein lipase activity
  - ↑ HDL production
- Ezetimibe
  - Inhibits cholesterol absorption
- Niacin
  - Unknown; may be due to ↓ VLDL/LDL synthesis
- Bile acid binding resins
  - ↑ fecal excretion of bile acids (Cl exchange for bile acids)
  - Depletes cholesterol, stimulating up-regulation of LDL
- Omega-3 fatty acids (fish oil)
  - Antithrombotic,antiinflammatory effects
  - Cardiac cell membrane stabilization
  - Inhibits IL-1, TNFα production

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DRUG	Effects	Side Effects	Contraindications
Statins	LDL ↓18-55% HDL ↑ 5-15% TG ↓ 7-30%	Myopathy	Liver disease Pregnancy
Bile Acid Sequestrants	LDL ↓ 15-30% HDL ↑ 3-5% TG ±	GI	TG > 200 mg/dl
Niacin	LDL ↓ 5-25% HDL ↑15-35% TG ↓20-50%	Gout, PUD ↑ BG	Chronic liver disease Severe gout

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DRUG	Effects	Side Effects	Contraindications
Fibric Acids	LDL ↓ 5-20% HDL ↑10-20% TG ↓20-50%	Dyspepsia	Severe renal/hepatic disease
Ezetimibe	LDL ↓18% HDL ↑ 3.5%	GI	Liver disease
Omega 3 Fatty Acids	TG ↓17-48% HDL ↑ 9%	GI LDL↑ Bleeding (↑↑ doses)	Pregnancy Fish allergies?

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DRUG	Drug Interactions
Atorvastatin	Caution with CYP3A4 inhibitors (macrolides, azole antifungals, verapamil, nefazodone, fluvoxamine, CyA, glyburide (↑ SDC 40%) fibrates, grapefruit juice; may ↑ digoxin SDC 40% ↓ renal function: no dose change
Fluvastatin	↑ phenytoin/warfarin SDCs; with glyburide, SDCs of both may ↑; ↓ renal function: no dose change
Lovastatin	Caution with CYP3A4 inhibitors (macrolides, azole antifungals, nefazodone, fluvoxamine, protease inhibitors, grapefruit juice; NTE 20 mg/day with niacin, gemfibrozil, CyA or NTE 40 mg/day with amiodarone, verapamil ↓ renal function: lower dose

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DRUG	Drug Interactions
Pravastatin	No CYP450 interactions; CyA may ↑ SDC caution with fibrates; ↓ renal function: no dose change
Rosuvastatin	No CYP450 interactions; ↓ dose with CyA, gemfibrozil; may ↑ INR with warfarin Asians and ↓ renal function: lower dose
Simvastatin	Avoid with macrolides, azole antifungals, nefazodone, protease inhibitors, grapefruit juice; caution: ≥ 1 gm/day niacin, fenofibrate; NTE 10 mg/day with gemfibrozil, CyA, danazol; NTE 20 mg/day with verapamil, amiodarone ↓ renal function: lower dose

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Which Statin?

- Consider cost
- If on other meds that inhibit CYP 3A4, 2C9 use statin with hepatic sulfation (pravastatin)
- If pt not at goal with one statin, doubling the dose decreases LDL 6%, so switch to a different statin
- Check fasting lipids/LFTs 6 to 12 wks after starting statin and repeat after dose adjustments (liver toxicity is dose-related)

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Which Statin?

- ↑ LFTs?
  - RARE but D/C and re-challenge with same or different statin when LFTs normalize
- Myositis risk - higher dose, interacting drugs, impaired renal function, small-framed, elderly
- Should CK levels be measured routinely?
  - Baseline and if problems

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Muscle Pain - What to Do?

- Lipophilic statins penetrate muscles more readily (simvastatin, atorvastatin, lovastatin)
- If muscle pain occurs, check CK, evaluate thyroid function, ask about exercise
- Switch to more hydrophilic statin (pravastatin, rosuvastatin, fluvastatin)

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Fibrates

- Drugs of choice for high triglycerides
- Gemfibrozil and fenofibrate now generic
- Fenofibrate less likely to interact with statins than gemfibrozil
  - Statin may need dose adjustment

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Bile Acid Resins

- Adjuncts to statins or niacin
- Principal effect is to ↓ LDL
- May ↑ triglycerides 7% with monotherapy
- Maximum bile acid synthesis occurs in the morning, so patients may take this then (can take the entire dose at one time)
- Take other meds 1 hour before or 4 hours after a bile acid resin
- Safety in pregnancy/children

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Niacin

- Most effective med for HDL ↑ (30%)
- May exacerbate gout, PUD, insulin resistance; consider in DM if pt is already on insulin
- Immediate release → ADRs (titrate slowly)
- Slow-release (inferior cholesterol lowering; ↑ hepatotoxicity due to prolonged hepatic exposure and less hepatocyte recovery time)
- Extended-release (as effective as immediate-release; less hepatotoxic than SR)
- In all cases, monitor LFTS

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Plant Sterols

- Marketed as margarine, salad dressing, snack bars
- Beta-sitosterol binds cholesterol in GI tract
- Co-administration of 1 g of beta-sitosterol with meal containing 500 mg cholesterol decreased cholesterol absorption 42%
- Clinical trials used 3 times/day dosing; decreased total cholesterol 8% and LDL cholesterol 14%

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Fish Oil Supplements

- Rich source of PUFA
- Option for patients with high triglycerides
- For patients who fail diet therapy/fibrates
- Dose-related effects
- One trial showed decreased mortality with 1 g/day
- Side effects: nausea, GI upset, fishy taste
- Use reliable supplement (USP verified) or use prescription (now called Lovaza®; formerly Omacor®)

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Risk Reduction

- Smoking cessation
- Aspirin (81 to 162 mg/day in most cases)
  - Type 2 DM and > 40 y/o or who have other risks (FH, HTN, smoking, hyperlipidemia, albuminuria)
  - Type 1 DM and > 40 y/o or other risks as in Type 2 DM
  - Consider in persons 30 to 40 y/o if other cardiovascular risk factors
- What if normal BP, but > 55 y/o ± HTN, but with other cardiovascular risks?
  - Consider an ACE inhibitor
  - If prior MI, beta blockers
- Evaluate cardiac risks before starting TZDs

ADA. *Diabetes Care.* 2007;30(suppl 1):S4-S41

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New Drugs

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Relatively New Agents

- Bolus insulin – Apidra® (glulisine; same use as Humalog and Novolog)
  - Use in Type 1 DM with basal insulin
  - Use in Type 2 DM
  - With oral agents, basal insulin
- Byetta® (exenatide)
  - Injectable agent that provides GLP-1 hormone, deficient in persons with type 2 diabetes
- Symlin® (pramlintide)
  - Injectable agent that replaces amylin, a hormone deficient in both type 1 and type 2 diabetes

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Exubera® (Inhaled Insulin)

- Bolus insulin
- Use in Type 1 DM with basal insulin
- Use in Type 2 DM
  - With oral agents, basal insulin
- Must have baseline lung function
  - Cannot use in smokers, severe lung disease
- Consider dosing
  - 1 mg = 3 Units of insulin
  - 3 mg = 8 Units of insulin

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2-Yr Study of Inhaled Insulin in T1DM

Parameters	Inhaled	Regular
ADRs	37.6%	13.1%
FPG↓ (mg/dL)	170 to 157 (13.3)	167 to 174 (6.6)
↓↓BG (events/subj mo)	2.8	4.1
Wt↑ (kg)	75.1 to 75.9 (0.8)	73.8 to 75.8 (2)
Ab (μU/mL)	4.5 to 64.5	4.5 to 3.85

Diabetes Care 2007;30:579-85

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Inhaled Insulin: What is Known

- Expensive (comparable to glitazones)
- Can't use in smokers/lung disease
- As effective as regular insulin
  - Limitation: all trials are open-label
  - Most patients in trials are White
- 2-yr lung safety information
- Fasting glucose lower
- Equivalent or less hypoglycemia than Reg
- Weight gain is minimal or less than Reg
- Patients prefer inhaled insulin

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Inhaled Insulin – the Unknown

- Significance of antibody formation?
- Beyond 2-yr lung safety information?
- What about postprandial glucose?
- Pharmacoeconomic data?
- Continued patient preference?

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DPP-IV Inhibitors

- Mechanism of action
  - Inhibit breakdown of GLP-1 and GIP
  - Hence, levels of GLP-1 and GIP rise, especially in response to meals
    - This inhibits glucagon
    - Stimulates endogenous insulin secretion when glucose is highest
  - Since these agents increase only glucose-stimulated insulin secretion, there is little risk of hypoglycemia

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Sitagliptin (Januvia®)

- Side effects
  - Headache
  - Nasopharyngitis
  - URI
- Drug Interactions
  - Studied in combination with SUs, metformin, pioglitazone
  - 38% protein bound
  - Does not inhibit or induce isoenzyme systems
    - Minor metabolism through CYP 3A4 and 2C8
  - Small ↑ in digoxin SDCs (11-18%)

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Sitagliptin (Januvia®)

- Dose 100 mg daily with or without food
- No dose adjustment in mild-moderate hepatic insufficiency
  - Not studied in severe hepatic impairment
- Dose adjustment in renal impairment
  - 50 mg daily for Cr Cl ≥ 30 to < 50 mL/min
    - Males: Cr > 1.7 to ≤ 3 mg/dL
    - Females: Cr > 1.5 to ≤ 2.5 mg/dL
  - 25 mg daily for Cr Cl < 30 mL/min
    - Males: Cr > 3 mg/dL
    - Females: Cr > 2.5 mg/dL
    - On dialysis

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Sitagliptin (Januvia®)

- Effects on A1c, BG, Weight
  - If A1c is ~8-9%
    - A1c ↓ 0.6 to 0.8%
  - If A1c is 9-10%
    - A1c ↓ 1.4%
  - FBG ↓ ~12 to 17 mg/dL
  - PPG ↓ ~ 50-60 mg/dL
  - Weight neutral

67 Does Rosiglitazone Increase Risk of MI and CV Mortality?

N Engl J Med 2007;356

- Meta analysis of 42 trials
  - N=15,560 pts on rosiglitazone
  - N=12,283 on other drugs
- MI (OR was 1.43; p=0.03)
  - 86 in rosiglitazone group
  - 72 in control group
- Death from CV causes (OR 1.43; p=0.06)
  - 39 in rosiglitazone group
  - 22 in control group

68 Does Rosiglitazone Increase Risk of MI and CV Mortality?

Issues

- 42 trials pooled that were not originally intended to explore CV outcomes; e.g. not powered to discern differences (if present)
- Total # of events was small
- Study could not control for previous risks of heart disease or prior CV events
- Confusion regarding stats – should have absolute risk increase; calculation not possible with info given (if one crunches the numbers, there is higher absolute risk of MI in the control group (0.618% vs 0.598%)

69 Does Rosiglitazone Increase Risk of MI and CV Mortality?

New interim analysis of RECORD

(Rosiglitazone evaluated for cardiac outcomes and regulation of glycemia in diabetes)

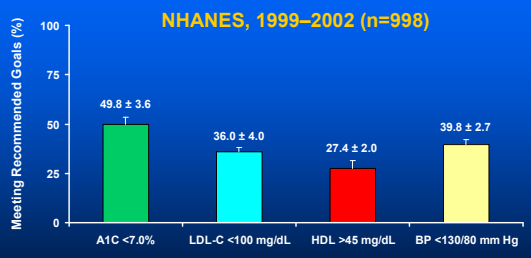
- 2220 pts assigned to receive add on rosiglitazone
- 2227 to receive combo of metformin + SU
- Primary end point: hospitalization or death from CV disease
- Mean F/U: 3.75 yrs

N Engl J Med 2007;357

70 Does Rosiglitazone Increase Risk of MI and CV Mortality?

- Results (HR 1.08; CI 0.89-1.31; pending adjudication HR: 1.11; CI 0.93-1.32)
  - 217 in rosi group achieved primary endpoint
  - 202 in control group achieved primary endpoint
- No significant differences between groups regarding MI and death from CV causes
- More pts with HF in rosi group (HR 2.15; CI 1.3-3.57)
- Interim findings are inconclusive regarding effect on overall risk of hospitalization or death from CV or all causes

71 Are Patients Meeting ADA Clinical Practice Recommendations?



ADA = American Diabetes Association; NHANES = National Health and Nutrition Examination Survey; A1C = glycosylated hemoglobin A1C; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure.
HDL >45 mg/dL = low risk.

Resnick HE et al. *Diabetes Care*. 2006;29:531-537.

72 2007 ADA Targets for Adults With T2DM

A1C	<7.0%*
Preprandial plasma glucose	90–130 mg/dL
Peak postprandial glucose	<180 mg/dL†
Blood pressure	<130/80 mm Hg
LDL-C	<100 mg/dL
Triglycerides‡	<150 mg/dL
HDL-C	>40 mg/dL (men) >50 mg/dL (women)

*Referenced to a nondiabetic range of 4.0%-6.0% using a DCCT assay; †Postprandial glucose measurements should be made 1-2 h after the beginning of the meal, generally peak levels in patients with diabetes; ‡Current NCEP/ATP III guidelines suggest that in patients with triglycerides ≥200 mg/dL, the "non-HDL cholesterol" (total cholesterol minus HDL) be used; the goal is ≤130 mg/dL.

ADA. *Diabetes Care*. 2007;30(suppl 1):S4-S41.